REMARKS

The Official Action dated June 4, 2003 has been carefully considered. Additionally, the telephone interview with the Examiner courteously afforded Applicants' representatives on November 19, 2003 is acknowledged and appreciated. The substance of the interview is discussed in detail below and is believed to have assisted in progression of prosecution. Accordingly, it is believed that the present application is now in condition for allowance. Reconsideration is respectfully requested.

Submitted herewith is a Second Declaration Under 37 C.F.R. 1.132 made by the inventors. The copy submitted herewith is unsigned, as the original Declaration is presently being executed by the co-inventors and will be submitted to the Examiner as soon as it is received by the undersigned. Consideration of the unsigned Declaration until the signed Declaration is submitted is respectfully requested.

In the Official Action, claims 1-3 and 5-34 were rejected under 35 U.S.C. §103(a) as being unpatentable over the Sangekar et al U.S. Patent No. 5,000,962 in view of the Stupak et al U.S. Patent No. 5,162,117 and the Zhang et al U.S. Patent No. 6,083,532. The Examiner asserted that Sangekar et al teach a long acting formulation which comprises a swellable polymer, examples of which include HPMC, HPC, HMC, HEC and HPC, and that a binder such as ethylcellulose may be employed. The Examiner acknowledged that Sangekar et al do not specifically teach the use of HPMC and HEC together in combination with EC. The Examiner relied on Zhang et al as disclosing a sustained release drug formulation including a pH independent gelling polymer comprising at least one of HPMC, HPEC, HPC and HEC. The Examiner asserted that Zhang et al therefore suggest that HPMC and HEC are known to be used in combination. The Examiner relied on Stupak et al as teaching the claimed excipients in a controlled release solid dosage tablet.

However, as discussed with the Examiner during the aforementioned interview, it is believed that the controlled release pharmaceutical compositions and processes for manufacture of such compositions as defined by independent claims 1, 14, 19, 23, 30, 33 and 34, and the claims dependent thereon, are nonobvious over and patentably distinguishable from the combination of Sangekar et al with Zhang et al and Stupak et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

The controlled release pharmaceutical compositions defined by claims 1, 14, 19, 30, 33 and 34 each require the combination of hydroxyethylcellulose (HEC) and hydroxypropylmethylcellulose (HPMC). Similarly, the process for the manufacture of a sustained release composition of pharmaceutically active substance defined by claim 23 employs the combination of HEC and HPMC. Claims 14, 19, 23, 30 and 34 further specify the combination of ethylcellulose (EC) in combination with the HEC and HPMC. As discussed with the Examiner during the interview, Applicants have discovered that a controlled release pharmaceutical composition with the claimed combination of HEC and HPMC provides both good immediate dosing of an active and good delayed dosing of the active. Such controlled release pharmaceutical properties are desirable with many actives, particularly high potency actives where immediate dosing of some, but not all, of the active is desired.

Sangekar et al disclose a long acting diltiazem formulation containing swellable hydrophilic polymers. Examples of the swellable hydrophilic polymers include: hydroxypropylmethylcellulose; hydroxypropylcellulose; methylcellulose; hydroxymethylcellulose; hydroxyethylcellulose; hydroxypropylcellulose, which can be used alone or in combination; carboxymethylcellulose and the sodium salt thereof, which can be used alone or in combination; and other hydrocolloids, such as acacia and guar gum (column 2, lines 57-64). As noted by the Examiner, Sangekar et al do not teach a combination of HEC

and HPMC as presently claimed. At best, Sangekar et al may suggest the equivalence of these various swellable hydrophilic polymers in their compositions.

As noted above, the Examiner has relied on Zhang et al as disclosing a combination of HEC and HPMC. Zhang et al disclose sustained release formulations containing three different types of polymers, namely a pH dependent gelling polymer, an enteric polymer and a pH independent gelling polymer. Zhang et al disclose at column 2, beginning at line 6, that the pH independent gelling polymer may be, for example, a hydroxyl propyl methyl cellulose, a hydroxyl propyl ethyl cellulose, a hydroxyl propyl cellulose, a hydroxyl ethyl cellulose, a methyl cellulose, a xantham gum or a polyethylene oxide. Each of the exemplary compositions of Zhang et al at column 3 containing the active verapamil HCl, at column 4 containing the active pentoxyfilline, and at column 4 containing the active nifedpine contains one pH independent gelling polymer. The Examiner noted that in claim 2, Zhang et al recite that the pH independent gelling polymer comprises at least one of a hydroxyl propyl methyl cellulose, a hydroxyl propyl ethyl cellulose, a hydroxyl propyl cellulose, a hydroxyl ethyl cellulose, a methyl cellulose, xantham gums, or a polyethylene oxide. Although the Zhang et al specification provides no teaching of a combination of pH independent gelling polymers, the Examiner has asserted that the recitation in claim 2 of "at least one of" the recited polymers provides a teaching of the use of the recited polymers in combination.

Applicants submit however that the recitation in claim 2 of at least one of the recited polymers, in the absence of any further teachings in the specification, does not suggest to one of ordinary skill in the art to use a combination of HEC and HPMC as presently claimed, or any desirability as to the use of such a combination. Nonetheless, at best, Zhang et al, like Sangekar et al, teach the equivalence of the listed pH independent gelling polymers in their compositions. Applicants have discovered however that HEC and HPMC are not equivalent for use in sustained release compositions and their use in combination provides

improvements over their individual use. In this regard, the Examiner's attention is first directed to the Declaration Under 37 C.F.R. 1.132 previously submitted in this application, particularly paragraph 3 and Table 2 set forth therein. Paragraph 3 describes the preparation of three compositions respectively containing 15% HPMC, 15% EC and 15% HEC. Table 2 set forth in the Declaration indicates that the dissolution rates of the three compositions were significantly different from one another, whereby the availability of active during dissolution of the respective compositions was significantly different. These results demonstrate that, ← arg 2 contrary to teachings of Sangekar et al and Zhang et al, HPMC, HEC and EC are not equivalent in controlled release compositions.

The Examiner's attention is also directed to the Second Declaration Under 37 C.F.R. 1.132 submitted herewith. The Second Declaration describes the preparation and study of three compositions containing a model drug and, respectively, (a) 10% HPMC in combination with 10% HEC, according to the invention, (b) 20% HPMC (comparative), and (c) 20% HEC (comparative). The dissolution rates of these three compositions are set forth at pages 2 and 3 of the Declaration. As is apparent, these results show differences in rate of dissolution when the same drug is formulated with (a) a combination of 10% HEC and 10% HPMC, versus (b) 20% HEC, or (c) 20% HPMC. For example, at one hour, 39.05% of the model drug was released from composition (a) containing the HEC/HPMC combination, while only 28.83% of the model drug was released from the composition (b) containing only HPMC, yet 98.15% was released from composition (c) containing only HEC. These differences in dissolution rates are significant, especially with high potency drugs where both ← arg 3 immediate and delayed release are necessary. Particularly, composition (a) according to the invention provides improved early dosing over composition (b) and improved delayed dosing over composition (c). The improved model drug release profile exhibited by composition (a) as compared with compositions (b) and (c) is neither taught nor suggested by either Sangekar

et al or Zhang et al, as these references do not teach or suggest any of HPMC, HEC or combinations of HPMC and HEC as having any differences in drug release profiles.

Thus, these Declarations show unexpected results provided by the presently claimed compositions as compared with the teachings of Sangekar et al and Zhang et al which, at best, teach equivalence of various polymers in their disclosed compositions. A prima facie case of obviousness can be rebutted by evidence of unexpected results, *In re Davis*, 177 U.S.P.Q. 381 (CCPA 1973). When an Applicant demonstrates substantial improved results and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary, *In re Soni*, 34 U.S.P.Q. 2d 1684 (Fed. Cir. 1995). The showings set forth in the Declarations show unexpected improvement and therefore rebut any prima facie case of obviousness established by the Examiner based on Sangekar et al and Zhang et al.

Finally, the Examiner has cited Stupak et al as disclosing the claimed excipients. However, as Applicants find no teaching or suggestion by Stupak et al of controlled release pharmaceutical compositions providing a combination of HPMC and HEC as presently claimed, or relating to the improvements provided by such a combination in a controlled release pharmaceutical combination, Stupak et al do not resolve the deficiencies of Sangekar el al and Zhang et al. It is therefore submitted that claims 1-3 and 5-34 are nonobvious over and patentably distinguishable from the combination of Sangekar et al, Zhang et al and Stupak et al, whereby the rejection under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

It is believed that the above and the Second Declaration Under 37 C.F.R. 1.132 submitted herewith places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Finally, during the aforementioned interview, the Examiner indicated that if there were any further outstanding issues in this application, she would telephone the undersigned to discuss any concerns. Applicants acknowledge and appreciate the Examiner's willingness to expedite any further prosecution in this application.

Respectfully submitted,

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